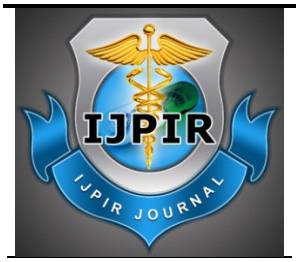
Research Article



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Current role of gmp audit for marketing authorization API

Ramala Achsah Sumedha*, P.Jyothi , Ramya Sri. S

Department of Regulatory Affairs, Holy Mary College of Pharmacy, Keesara, ghatkesar, Telanagana 501301, India
Sura Pharma Labs, Dilsukhnagar, Hyderabad, Telangana-500060, India

ABSTRACT

In this type of work a comparative study on marketing authorization application (MAA) representation for Preparation of Drug master files (DMF) in Europe for Active pharmaceutical ingredient (API) was reviewed thoroughly. The MAA representation DMF is required. This document provides the regulatory authority with confidential information regarding facilities, processes in a manufacturing unit. In this work all types in a DMF is included. The work focused on the preparation of DMF's for API. The dossier required for the CTD also included. The data required for DMF with their serial classes are mentioned. The study on EDMF and the particulars are listed.

Key words: CTD, EDMF, EMEA, MAA.

INTRODUCTION

Introduction to regulatory affairs in pharmaceutical industry

Introduction to regulatory affairs

Regulatory Affairs (RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods). Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents.

Importance of regulatory affairs

In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company.

Inadequate reporting of data may prevent a timely positive evaluation of marketing application. A new drug may have cost many millions of pounds, Euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse1 failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients.

A good Regulatory Affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavor with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources.

Ramala Achsah Sumedha
Department of Regulatory Affairs , Holy Mary College of Pharmacy ,
Keesara ,ghatkesar, Telanagana 501301, India

Marketing authorization applications can be classified broadly in three groups, which Comprise applications for

1) Products containing new chemical or biological active pharmaceutical ingredients (APIs);
2) *Multisource pharmaceutical products (generic products):* that is, new marketing authorization holders, formulations, or sources of *well established drugs*;
3) Variations to existing marketing authorizations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR: Department of Pharma Quality Assurance, MCOPS, Manipal
2. DATE OF SUBMISSION: 11/21/2005
3. ADDRESS *(Number, Street, City, State and Zip Code)*: Dept. of QA,MCOPS, Manipal, Karnataka, ZIP: 576104 . Country .. India
4. TELEPHONE NUMBER *(Include Area Code)*: 082054545454
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*: Atropine
6. IND NUMBER *(If previously assigned)*: 634582
7. INDICATION(S) *(Covered by this submission)*: Corneal Ulcer
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☑ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER *(Specify)*
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION: 1 6,946,297
10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*** SERIAL NUMBER: 0
11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☑ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☑ NEW PROTOCOL	☑ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☑ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☑ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (3/05) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2

Figure 1: Investigational New Drug Application

Audit Options are acceptable to the European Authorities

- The Customer / Supplier Audit or **Second Party Audit** that would be performed by the Qualified Auditors of the for API Manufacturer.

The audit may also be performed by the Qualified Auditors of the Marketing Authorization Holders, for example in the case where the Marketing Authorization Holder is responsible for the Manufacture or Supply of the API and contracts out the manufacture of the Medicinal.

In this case, the responsibilities for auditing of the API Manufacturer should be defined in the Technical Contract between the Marketing and Manufacturing Authorization Holders.

A **Third Party Audit** of the API Manufacturer performed on behalf of the Qualified Person(s) or responsible person. The Qualified Person or responsible person (Contract Giver) confirms that the Third Party Audit Process provides an effective assessment of the GMP status of the API manufacturer and that the audit is performed by independent, qualified Auditors with no conflict of interest.

Shared Third Party Audits are acceptable to the European Authorities as long as the Qualified Person(s) ensures that the scope of the audit is applicable to each Medicinal Product that uses the API as Starting Material.
A Third Party Audit can either be initiated by one or more Manufacturing Authorization Holder(s) ('called 'customer') or by the API Manufacturer / Distributor / Broker / Importer/ Packer / Re-Packer itself (called 'Auditee').
If the API Manufacturer / Distributor / Broker/ Importer/ Packer / Re-Packer initiate the audit, the purpose of the audit is a self assessment of the GMP status of the API Manufacturer.
The API manufacturers may use such audit programmers beyond the EU QP requirements as part of their own API supplier qualification management.
In the opinion of the Ad Hoc GMP Inspection Services meeting of EU Inspectors organized by EMA, the Manufacturing Authorization Holders should decide for themselves whether there are any conflict of interest issues with any Third Party Audit Option.

APIC Audit Program

The approach taken by many Medicinal Product Manufacturers towards this legal requirement is to perform one to one audits of their API manufacturers. However it is recognized that audits are time-consuming and expensive for both the API and Medicinal Product Manufacturer and there is potential for significant audit overload for the Pharmaceutical Industry if this is the only option used.

Critical Deficiency: Deficiency which has produced, or leads to a significant risk of producing an Active Pharmaceutical Ingredient that could be harmful to the human or veterinary patient.

Major Deficiency

A non critical deficiency which has produced or may produce a product, which does not comply with its marketing authorization or which indicates a major deviation from EU Good Manufacturing Practice, or a combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such

Other Deficiency

A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.

The Auditors

Educational Background and Experience

The Auditors should have a good educational knowledge of chemistry. Qualifications as Pharmacist, Medical Doctor, Chemical Engineer, graduate or Ph.D. in Chemistry, Biology or related fields as Agro chemistry etc., are appropriate. A good understanding of biochemistry and analytical techniques and practices is a definite advantage.
At least 5 years practical experience of GMP manufacture of Active Pharmaceutical Ingredients may also be considered as sufficient knowledge and background.
With the exception of Pharmacists whose university courses may include modules on GMP Regulations, a good knowledge of applicable regulations is usually obtained through training and experience.

Auditor Training Courses for 'Certification'

Attendance at a specific five-day training course sponsored by APIC (two and a half days related to GMPs in API manufacture and two and a half days for training in effective auditing techniques) is a prerequisite for becoming an APIC Certified Auditor. The participant will receive a certificate of attendance for each of the two training courses.

Certification of Auditors

In order to become an APIC Certified Auditor, the Auditor has to undergo an examination. This examination consists of 2 parts.
Part 1: The participant has to take a written exam on the contents of the GMP-compliant manufacture of APIs in accordance with ICH Q7. This written exam is created by APIC in co-operation with the API Compliance Institute. After the training course, the participant is given access to a total of 30 questions via the Internet. These have to be answered following the multiple-choice procedure. For this task, the participant has 60 minutes. He/she has passed the exam if 70% of the questions have been answered correctly. In case of failure, the exam can be repeated twice. The costs have to be borne by the participant.
Part 2: An APIC representative who is a trainer in the course and a trainer with academic education in psychology assess the auditing skills of the participants during the Training Course.
The APIC representative judges the participant's ability to conduct audits within the framework of the APIC Auditing Programme. The psychologist assesses the verbal and non-verbal communication, analyses the art of questioning and conversation techniques as well as the behaviour in conflict situations. These ratings are put down on a form including a statement whether or not the trainee auditor should become an APIC Certified Auditor and the form is archived at the API Compliance Institute together with the record of performance in the examination (Part 1).
The records are kept as long as the Auditor maintains his/her certification. Afterwards the records are archived for another 7 years.
Auditors who have successfully passed Part 1 and Part 2 will then become APIC Certified Auditors. The Certificate is valid for three years.
Those Auditors who would like to become active within the framework of the APIC Auditing Programme have to indicate this together with their proof of educational qualification and experience (see point 2.1.) on the application form for the training course.

The API Compliance Institute keeps a register of all APIC Certified Auditors

The Auditor's certification can be extended for subsequent three year periods provided he/she has attended at least two recognized training courses / conferences on current GMP Topics and has satisfactorily performed at least three audits during the current period of certification.
If either of these conditions is not met, the Auditor's name will be withdrawn from the register of APIC Certified Auditors.
All current APIC Certified Auditors will be required to take the examination test at the time of their next Re-Certification.

Contract

Auditors who qualify to become 'APIC Certified Auditors' and who agree to conduct audits in the framework of the APIC Audit Programme have to sign a contract with the API Compliance Institute . This contract lays down the obligations of the Certified Auditor.

The Audit Process

Steps of the Audit Process

The following section describes the steps that should be followed in the audit process from the initial contact with the API Compliance Institute by the potential customer until the distribution of the audit report.

A. Preliminary Talks (details see 3.1.1) 1 month
B. Preparation for the audit (details see 3.1.2) 1 month in parallel with preliminary talks and selection
C. Selection of Auditors (details see 3.1.3)1 month in parallel with the preparation and preliminary talks
D. Signing of Audit Contract, 2 weeks
E. Execution of the Audit (details see 3.1.4.)
F. Audit Report, Reviewing, Signing and Archiving (details see 3.1.5.)
G. Audit Follow Up (details see 3.2)

Relationship between APIC and the API Compliance Institute

There is an Agreement between APIC and the API Compliance Institute that defines the responsibilities of each party (Table 1)

Table 1

API Compliance Institute	APIC
Design of the Auditor qualification seminars	Providing speakers for the Auditor training courses;
Organization and execution of the qualification seminars and examinations for Certified Auditors	Involvement of APIC Executive and Quality Working Group members in Auditor training courses
Maintenance of Current list of APIC Certified Auditors	APIC lead representative for audit programme to be involved in Auditor qualification courses and to evaluate suitability of candidates for APIC Certified Auditors
Coordination of the APIC Third Party audits	
Steps of the audit process: - Preliminary Talks - Preparation for the audit - Selection of Auditors	APIC lead representative for Audit programme or APIC EXEC Member to give independent review of any serious objections from the Auditee / customer to GMP Deficiencies and classifications - at the request of API Compliance Institute
Administration and archiving of the audit reports for 7 years	
Compilation of an annual report for APIC	

Active pharmaceutical ingredient (API)

An active ingredient is any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.
(USFDA Glossary of terms, it can be found in line at Drugs@FDA Glossary of Terms).

Market Authorization Holder

Is a person resident/domicile to each of the EAC Partner States who holds authorization to place a medicinal product in the EAC Partner Sates and is responsible for that product.

Commitment batches

Production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Comparator product

A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established.

Generic product

Is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labeling. (WHO glossary of terms).

Innovator medicinal product

Generally the medicinal product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality.

CONCLUSION

In pharmaceutical industries the API is having a key role for preparation of drug substances. It helps to maintain quality by innovation of new drugs into the market which finally ensures the safety and efficacy to protect public health. The Manufacturing Authorization holder is responsible for taking appropriate action to ensure API sources are GMP compliant. Adverse findings from inspections may result in various action steps taken by EMEA. In general since the introduction of the new legislation dose form manufacturers are taking steps to assure GMP compliance of the API supply chain.

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